Available online at www.sciencedirect.com

ScienceDirect

Procedia Computer Science 102 (2016) 333 – 341

Procedia Computer Science

12th International Conference on Application of Fuzzy Systems and Soft Computing, ICAFS 2016, 29-30 August 2016, Vienna, Austria

Global stability analysis of oseltamivir–resistant influenza virus model

Bilgen Kaymakamzade[a], Isa Abdullahi Baba[a,*], Evren Hincal[a]

[a,*] *Department of Mathematics, Near East University, P.O.BOX:99138, Nicosia, North Cyprus, Mersin 10 Turkey*

Abstract

We study a new model describing the dynamics of both Oseltamivir resistant and non- resistant Influenza virus. Incorporated in the model is oseltamivir drug for the non- resistant strain and nalidixic acid or dorzolomide drugs for the resistant strain. The basic reproduction ratios R_0 are determined using the next generation matrix. The local and global asymptotic stability of the disease free equilibrium are determined and shown to only exist if $R01 \leq 1$ and $R02 \leq 1$. Local and global asymptotic stability of the endemic equilibria exist if $R01 > 1$ and $R02 > 1$. Lyapunov function was used to show the global stabilities.

Peer-review under responsibility of the Organizing Committee of ICAFS 2016

Keywords: Oseltamivir; nalidixic acid; dorzolomide; h1n1 influenza virus; next generation matrix; lyapunov function; basic reproduction ratio.

1. Introduction

Influenza viruses are segmented, negative- sense, enveloped RNA viruses[1]. Influenza virus is of three types A, B and C. These types can be distinguished by serological responses to their internal proteins. Influenza A has antigenic variability which allows it to escape neutralization from anti- bodies[2]. Influenza B also exhibits antigenic variability property, but less than that of A. This property is not common in influenza C, hence influenza A is more serious than B, and then C[3].

Influenza A virus is divided into *hemagglutinin* (H) and *neuraminidase* (N) based on the two proteins on the surface of the virus. Hemagglutinin are divided into eighteen types (H1 to H18) and neuraminidase into eleven

* İsa Abdullahi Baba.
E-mail address: isa.baba@neu.edu.tr

Peer-review under responsibility of the Organizing Committee of ICAFS 2016
doi:10.1016/j.procs.2016.09.409

subtypes (N1 to N11). It can also be divided into different strains, most popular strains found in people are H1N1 and H3N2 viruses[4]. The pandemic of influenza A (H1N1) reach its peak with the evolution of drug- resistant H1N1 strain[5].

Oseltamivir also known as Tamiflu is the most widely used anti- influenza drug[3]. Nowadays, there is emergence of Oseltamivir- resistant H1N1 influenza viruses, which is as a result of natural genetic drift and drug treatment[6].

Oseltamivir- resistant influenza virus can exist before or rapidly emerge during drug antiviral therapy[7]. Ju Bao et al.[3], proposed the use of drugs that are structurally similar to Oseltamivir as anti- Oseltamivir resistant influenza drugs. The drugs proposed are *nalidixic acid* and *dorzolamide*.

Mathematical models play vital roles in describing the transmission of both drug - resistance and non-resistance influenza viruses in a population[8,9,10]. Most of these models are of the SEIR form[5]. Global stability analysis of some of these models can be found in literature[11,12].

In this paper we consider a new SEIR model describing the dynamics of both oseltamivir resistance and non-resistance Influenza. Incorporated in the model is the use of oseltamivir drug for the non – resistance virus and nalidixic acid and dorzolamide drugs for the case of oseltamivir- resistance virus. Threshold quantities known as basic reproduction ratios R_0^1 and R_0^2 are found using next generation matrix. It is also shown that, $R_0^i \leq 1$, (i=1,2), the disease free equilibrium E_0 is both locally and globally asymptotically stable and the disease dies out. Whereas if $R_0^i > 1$ (i=1,2), the endemic equilibriums are both locally and globally asymptotically stable and epidemics occur.

The paper is organized as follows: In chapter 2 the model is formulated, equilibria and basic reproduction ratios are also determined. Section 3 deals with local and global stabilities of DFE. Section 4 deals with local and global stabilities of the endemic equilibria. Conclusions are given in chapter 5.

2. Model Formulation

2.1. Construction of the Model

The transmission of both oseltamivir resistance and non- resistance influenza virus is considered. Also we incorporate the use of Oseltamivir drug for the non-resistance virus and the use of nalidixic acid and dorzolamide drugs for the oseltamivir- resistance virus. The population N(t) is divided into six compartments by modifying the conventional SEIR model. The compartments are S, E_R, I_R, E_u, I_u and R, which denotes the sizes of suspectible, infected but not infective oseltamivir- resistant, infectious oseltamivir resistant, infected but not infective non-resistant, infectious to non-resistant, and removed compartments respectively. We assume recruitment rate and natural death rate only in the susceptible compartment. The model is given by a system of ordinary differential equations:

$$\frac{dS}{dt} = \Lambda - \alpha S I_R - \beta S I_U - ds$$

$$\frac{dE_R}{dt} = \alpha S I_R - kE_R$$

$$\frac{dI_R}{dt} = k(1-p)E_R - \mu I_R$$

$$\frac{dE_U}{dt} = \beta S I_U - mE_U$$

$$\frac{dI_U}{dt} = m(1-q)E_U - \gamma I_U$$

$$\frac{dR}{dt} = mqE_U + \gamma I_U + \mu I_R + kpE_R$$

Where Λ is a constant recruitment rate and d is natural death rate which is only through the susceptible compartment, α is a contact rate of oseltamivir- resistant virus, β is contact rate of non-resistant virus, kp and $k(1-p)$ are the rate at which people that are exposed to oseltamivir resistant become recovered and infectious respectively, mq and $m(1-q)$ are the rate at which people that exposed to non - resistant virus become recovered and infectious respectively, μ is the rate at which infectious to oseltamivir resistant virus become recovered by taking *nalidixic acid* or *dorzolomide* drugs, γ is the rate at which infectious to non-resistant virus become recovered by taking oseltamivir drug. It follows that;

$$\frac{dN}{dt} = \left(S + E_R + I_R + E_U + I_U + R\right)' = \Lambda - dS$$

$$\lim_{\sup t \to \infty} \left(S + E_R + I_R + E_U + I_U + R\right) \le \frac{\Lambda}{d}$$

Therefore the possible region for (1) is ;

$$\Omega = \left\{ \left(S, E_R, I_R, E_U, I_U, R\right) : S > 0, E_R \ge 0, I_R \ge 0, E_U \ge 0, I_U \ge 0, S + E_R + I_R + E_U + I_U + R \le \frac{\Lambda}{d} \right\}$$

It is obvious that Ω is positively invariant with respect to (1).

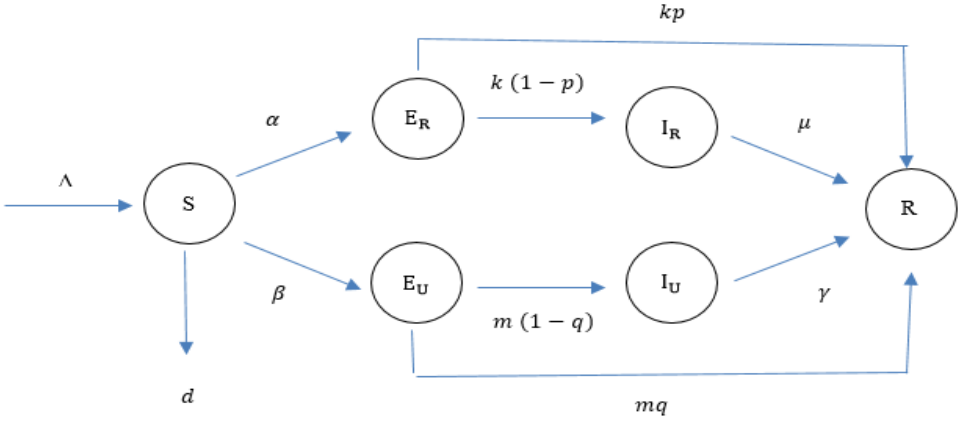

Fig. 1.: Transfer diagram of model (1)

2.2. Equilibria

Setting the equations in (1) equal to zero, and solving simultaneously we get three equilibrium points:

i) Disease free equilibrium,

$$E_0 = \left(\frac{\Lambda}{d}, 0, 0, 0, 0\right)$$

ii) non-resistance virus free equilibrium,

$$E_1 = \left(\frac{\mu}{\alpha(1-p)}, \frac{\alpha\Lambda - \alpha\Lambda p - \mu d}{\alpha k(1-p)}, \frac{\alpha\Lambda - \alpha\Lambda p - \mu d}{\alpha\mu}, 0, 0 \right)$$

iii) Oseltamivir - resistance virus free equilibrium,

$$E_2 = \left(\frac{\gamma}{\beta(1-q)}, 0, 0, \frac{\beta\Lambda - \beta\Lambda q - \gamma d}{\beta m(1-q)}, \frac{\beta\Lambda - \beta\Lambda q - \gamma d}{\beta\gamma} \right)$$

2.3. Basic Reproduction Ratio

Basic reproduction ratio (R_0) is the number of secondary infections caused by one infectious individual in a wholly susceptible population. We use the next Generation matrix as used in[13] to determine the R_0.

$$f = \begin{bmatrix} \alpha S I_R \\ 0 \\ \beta S I_U \\ 0 \end{bmatrix} \quad v = \begin{bmatrix} kE_R \\ \mu I_R - k(1-p)E_R \\ mE_U \\ \gamma I_U - m(1-q)E_U \end{bmatrix} \quad F = \begin{bmatrix} 0 & \alpha S & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \beta S \\ 0 & 0 & 0 & 0 \end{bmatrix} \quad V = \begin{bmatrix} k & 0 & 0 & 0 \\ -k(1-p) & \mu & 0 & 0 \\ 0 & 0 & m & 0 \\ 0 & 0 & -m(1-q) & \gamma \end{bmatrix}$$

$$FV^{-1} = \begin{bmatrix} \frac{\alpha S(1-p)}{\mu} & \frac{\alpha S}{\mu} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{\beta S(1-q)}{\gamma} & \frac{\beta S}{\gamma} \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

The eigenvalues are

$$\lambda_1 = \lambda_2 = 0 \quad \lambda_3 = \frac{\alpha S(1-p)}{\mu}, \lambda_4 = \frac{\beta S(1-q)}{\gamma}$$

Therefore, the spectral radius $P(FV^{-1})$ is $\frac{\alpha S(1-p)}{\mu}$ and $\frac{\beta S(1-q)}{\gamma}$.

Hence we have, $R_0^1 = \frac{\alpha S(1-q)}{\mu}, R_0^2 = \frac{\beta S(1-q)}{\gamma}$

3. Local and Global Stability of DFE

In this chapter local and global stability of the disease free equilibrium are found.

3.1. Local Stability of the Disease Free Equilibrium

Theorem 1: E_0 is locally asymptotically stable if $R_0^1 \le 1$ and $R_0^2 \le 1$, unstable otherwise.

Proof: Jacobian matrix at E_0 is given as,

$$J(E_0) = \begin{bmatrix} -d & 0 & -\alpha S^* & 0 & -\beta S^* \\ 0 & -k & \alpha S^* & 0 & 0 \\ 0 & k(1-p) & -\mu & 0 & 0 \\ 0 & 0 & 0 & -m & \beta S^* \\ 0 & 0 & 0 & m(1-q) & -\gamma \end{bmatrix}$$

Eigenvalues of $J(E_0)$ are

$\lambda_1 = -d$, $\lambda_2 = -\gamma$

$\lambda_3 = -\frac{1}{2}k - \frac{1}{2}\mu + \frac{1}{2}\sqrt{-4S\alpha kp + 4S\alpha k + k^2 - 2\mu k + \mu^2}$, $\lambda_4 = -\frac{1}{2}k - \frac{1}{2}\mu - \frac{1}{2}\sqrt{-4S\alpha kp + 4S\alpha k + k^2 - 2\mu k + \mu^2}$

$\lambda_5 = -\frac{1}{2}m - \frac{1}{2}\gamma + \frac{1}{2}\sqrt{-4S\beta mq + 4S\beta m + \gamma^2 - 2\gamma m + m^2}$, $\lambda_6 = -\frac{1}{2}m - \frac{1}{2}\gamma - \frac{1}{2}\sqrt{-4S\beta mq + 4S\beta m + \gamma^2 - 2\gamma m + m^2}$,

Taking

$$\lambda_3 = -\frac{1}{2}k - \frac{1}{2}\mu + \frac{1}{2}\sqrt{-4S\alpha kp + 4S\alpha k + k^2 - 2\mu k + \mu^2} = \frac{1}{2}\left[-(k+\mu) + \sqrt{(\mu+k)^2 - 4\left[\mu k\left(1 - R_0^1\right)\right]}\right] < 0$$

If,

$$(\mu + k)^2 - 4\mu k\left(1 - R_0^1\right) < (\mu + k)^2 \Rightarrow \mu k\left(1 - R_0^1\right) > 0 \Rightarrow R_0^1 < 1$$

$$\lambda_4 = -\frac{1}{2}k - \frac{1}{2}\mu - \frac{1}{2}\sqrt{-4S\alpha kp + 4S\alpha k + k^2 - 2\mu k + \mu^2} = -\frac{1}{2}\left[(\mu + k) + \sqrt{(\mu + k)^2 - 4\mu k\left(1 - R_0^1\right)}\right]$$

To show that

$\sqrt{(\mu+k)^2 - 4\mu k\left(1-R_0^1\right)}$ is not complex it is enough to show that $(\mu+k)^2 - 4\mu k\left(1-R_0^1\right) > 0$,

$(\mu+k)^2 - 4\mu k\left(1-R_0^1\right) = (\mu-k)^2 4\mu k R_0^1 > 0$, since $(\mu-k)^2 > 0$

Similarly, λ_5 and λ_6 can be shown to be negative by following the same procedure if $R_0^2 \le 1$.

3.2. Global Stability of the Disease Free Equilibrium

Theorem 2: If $R_0^1 \le 1$ and $R_0^2 \le 1$, then the DFE E_0 is globally asymptotically stable in Ω.

Proof: We construct the following Lyapunov function

$$V(t) = kI_R + k(1-p)E_R + \mu I_U + m(1-q)E_U > 0$$

$$\dot{V} = k\dot{I}_R + k(1-p)\dot{E}_R + \mu\dot{I}_U + m(1-q)\dot{E}_U$$

$$= k\left[k(1-p)E_R - \mu I_R\right] + k(1-p)\left[\alpha S I_R - kE_R\right] + m\left[m(1-q)E_U - \gamma I_U\right] + m(1-q)\left[\beta S I_U - mE_U\right]$$

$$= kI_R\left(-\mu + (1-p)\alpha S\right) + mI_U\left(-\gamma + (1-q)\beta S\right) = -kI_R\mu\left(1 - \frac{(1-p)\alpha S}{\mu}\right) - mI_U\gamma\left(1 - \frac{(1-q)\beta S}{\gamma}\right) = -kI_R\mu\left(1 - R_0^1\right) - mI_U\gamma\left(1 - R_0^2\right) < 0$$

If $R_0^1, R_0^2 < 1$.

$\dot{V} = 0$ iff $S = N, E_R = E_U = I_R = I_U = 0$. Hence by Lasalle invariance principle E_0 is globally asymptotically stable in Ω when R_0^1, $R_0^2 \le 1$.

4. Local and Global Stability of Endemic Equilibria

In this chapter local and global stability of the endemic equilibria are found.

4.1. Local and Global Stability of E_1

Theorem 3: The endemic equilibrium E_1 is locally asymptotically stable in Ω for $R_0^1 > 1$.

Proof

$$E_1 = \left(\frac{\mu}{\alpha(1-p)}, \frac{\alpha\Lambda - \alpha\Lambda p - \mu d}{\alpha k(1-p)}, \frac{\alpha\Lambda - \alpha\Lambda p - \mu d}{\alpha\mu}, 0, 0 \right)$$

$$S_1 = \frac{S_0}{\dfrac{\alpha(1-p)S_0}{\mu}} = \frac{S_0}{R_0^1} > 0$$

$$E_{R1} = \frac{\alpha\Lambda p - \alpha\Lambda + d\mu}{-\alpha k(1-p)} = \frac{\Lambda}{k} - \frac{dS^*}{k}\frac{1}{\dfrac{\alpha(1-p)S^*}{\mu}} = \frac{\Lambda}{k} - \frac{dS^*}{k}\frac{1}{R_0^1}$$

$$E_{R1} = \frac{\alpha\Lambda p - \alpha\Lambda + d\mu}{-\alpha k(1-p)} = \frac{\Lambda}{k} - \frac{d}{k}\frac{\Lambda}{d}\frac{1}{R_0^1} = \frac{\Lambda}{k}\left(1 - \frac{1}{R_0^1}\right) = \frac{\Lambda}{kR_0^1}\left(R_0^1 - 1\right) > 0$$

If $R_0^1 > 1$

$$I_{R1} = \frac{\alpha\Lambda - \alpha\Lambda p - \mu d}{\alpha\mu} = \frac{\Lambda}{\alpha S^*}\frac{\alpha S^*(1-p)}{\mu} - \frac{d}{\alpha} = \frac{\Lambda}{\alpha S^*}R_0^1 - \frac{d}{\alpha} = \frac{d}{\alpha}\left(R_0^1 - 1\right) > 0$$

If $R_0^1 > 1$.

Theorem 4: If $R_0^1 > 1$, then the endemic equilibrium E_1 is globally asymptotically stable.

Proof: We define a Lyapunov function V as follows;

$$V = \left(S - S^* - \ln\frac{S}{S^*} \right) + \left(E_R - E_R^* - \ln\frac{E_R}{E_R^*} \right) + \left(I_R - I_R^* - \ln\frac{I_R}{I_R^*} \right)$$

$$\dot{V} = \dot{S}\left(1 - \frac{S^*}{S}\right) + \dot{E}_R\left(1 - \frac{E_R^*}{E_R}\right) + \dot{I}_R\left(1 - \frac{I_R^*}{I_R}\right)$$

Consider, $$\dot{S}\left(1 - \frac{S^*}{S}\right) = \left(\Lambda - \alpha S I_R - \beta S I_U - dS\right)\left(1 - \frac{S^*}{S}\right)$$

Since, $$\Lambda = \alpha S_1 I_R + \beta S_1 I_U + dS_1 \text{ and}$$

$S^* = \dfrac{\mu}{\alpha(1-p)}$

$$\dot{S}\left(1-\frac{S_1}{S}\right)=\left(\alpha S_1 I_{R1}+\beta S_1 I_{U1}+dS_1-\alpha SI_R-\beta SI_U-dS\right)\left(1-\frac{\mu}{\alpha(1-p)S}\right)\le-\left[\alpha\left(SI_R-S_1I_{R1}\right)+\beta\left(SI_U-S_1I_{U1}\right)-d\left(S-S_1\right)\right]\left(1-\frac{1}{R_0^1}\right)$$

$$=-\left[\alpha\left(SI_R-\frac{\mu}{\alpha(1-p)}\frac{\alpha\Lambda(1-p)-\mu d}{\alpha\mu}\right)+\beta\left(SI_U-0\right)-d\left(S-\frac{\mu}{\alpha(1-p)}\right)\right]\left(1-\frac{1}{R_0^1}\right)\le-\left[\alpha SI_R-S_0d+\frac{\mu d}{\alpha(1-p)}+\beta SI_U+dS\left(1-\frac{1}{R_0^1}\right)\right]\left(1-\frac{1}{R_0^1}\right)$$

$$=-\left[\alpha SI_R+\beta SI_U-\left(S_0d-\frac{\mu d}{\alpha(1-p)}\right)+dS\left(1-\frac{1}{R_0^1}\right)\right]\left(1-\frac{1}{R_0^1}\right)=-\left[\alpha SI_R+\beta SI_U+d\left(S-S_0\right)\left(1-\frac{1}{R_0^1}\right)\right]\left(1-\frac{1}{R_0^1}\right)<0$$

If $R_0^1>1$.

$$\dot{E}_R\left(1-\frac{E_{R1}}{E_R}\right)=\left(\alpha SI_R-kE_R\right)\left(1-\frac{E_{R1}}{E_R}\right)=\alpha SI_R-kE_R-\frac{I_R}{E_R}\alpha SE_{R1}+kE_{R1}$$

$$=\alpha SI_R-kE_R-\frac{I_R}{E_R}\alpha S\frac{\alpha\Lambda(1-p)-\mu d}{\alpha k(1-p)}+k\frac{\alpha\Lambda(1-p)-\mu d}{\alpha k(1-p)}=\alpha SI_R-kE_R-\frac{\Lambda}{k}\left(\frac{I_R}{E_R}\alpha S-k\right)\left(1-\frac{1}{R_0^1}\right)$$

$$=\alpha SI_R-kE_R-\frac{\Lambda}{k}\left(I_R\alpha S-E_Rk\right)\left(1-\frac{1}{R_0^1}\right)=\left(I_R\alpha S-E_Rk\right)\left(1-\frac{\Lambda}{k}\left(1-\frac{1}{R_0^1}\right)\right)<0$$

If

$$1<\frac{\Lambda}{kE_R}\left(1-\frac{1}{R_0^1}\right)\Rightarrow R_0^1>\frac{1}{\left(1-\frac{kE_R}{\Lambda}\right)}>1$$

Lastly,

$$\dot{I}_R\left(1-\frac{I_{R1}}{I_R}\right)=\left(k(1-p)E_R-\mu I_R\right)\left(1-\frac{I_{R1}}{I_R}\right)=k(1-p)E_R-\mu I_R-\frac{E_R}{I_R}k(1-p)I_{R1}+\mu I_{R1}$$

$$=k(1-p)E_R-\mu I_R-\frac{E_R}{I_R}\left(\frac{\Lambda k}{\alpha S_0}\frac{(1-p)\alpha S_0}{\mu}-\frac{k(1-p)d}{\alpha}\right)+\frac{\Lambda}{\alpha}\frac{\alpha(1-p)}{\mu}-\frac{\mu d}{\alpha}$$

$$=k(1-p)E_R-\mu I_R-\frac{E_R}{I_R}\frac{dk}{\alpha}\left(R_0^1-1\right)(1-p)+\frac{\mu d}{\alpha}\left(R_0^1-1\right)$$

$$=k(1-p)E_R-\mu I_R-\left(\frac{E_R}{I_R}\frac{dk}{\alpha}(1-p)-\frac{\mu d}{\alpha}\right)\left(R_0^1-1\right)=\left(k(1-p)E_R-\mu I_R\right)\left(1-\frac{d}{\alpha I_R}\left(R_0^1-1\right)\right)<0$$

If

$$1<\frac{d}{\alpha I_R}\left(R_0^1-1\right)\Rightarrow R_0^1>1+\frac{\alpha I_R}{d}>1 \text{ since } \frac{\alpha I_R}{d}>0$$

This implies if $R_0^1>1$ then E_1 is globally asymptotically stable.

4.2. Local and Global Stability of E_2

Theorem 5: The endemic equilibrium E_2 is locally asymptotically stable in Ω for $R_0^2 > 1$.

Proof

$$E_2 = \left(\frac{\gamma}{\beta(1-q)}, 0, 0, \frac{\beta\Lambda - \beta\Lambda q - \gamma d}{\beta m(1-q)}, \frac{\beta\Lambda - \beta\Lambda q - \gamma d}{\beta\gamma} \right)$$

$$S_2 = \frac{\gamma}{\beta(1-q)} = \frac{S^*}{\frac{\beta S^*(1-q)}{\gamma}} = \frac{S^*}{R_0^2}$$

$$E_{U2} = \frac{\beta\Lambda - \beta\Lambda q - \gamma d}{\beta m(1-q)} = \frac{\beta\Lambda(1-q)}{\beta m(1-q)} - \frac{\gamma d}{\beta m(1-q)} = \frac{\Lambda}{m} - \frac{d}{m}\frac{S^*}{R_0^2}$$

Since, $S^* = \frac{\Lambda}{d}$ then, $E_{U2} = \frac{\Lambda}{m}\left(1 - \frac{1}{R_0^2}\right) > 0$ if $R_0^2 > 1$.

$$I_{U2} = \frac{\beta\Lambda - \beta\Lambda q - \gamma d}{\beta\gamma} = \frac{\beta\Lambda(1-q)}{\beta\gamma} - \frac{\gamma d}{\beta\gamma} = \frac{\Lambda}{\beta S^*}\frac{\beta S^*(1-q)}{\gamma} - \frac{d}{\beta} = \frac{d}{\beta}\left(R_0^2 - 1\right) > 0$$

If $R_0^2 > 1$

Theorem 6: If $R_0^2 > 1$, then the endemic equilibrium E_2 is globally asymptotically stable.

Proof: The proof is similar to the global stability of E_1, with $R_0^1 > 1$ replaced by $R_0^2 > 1$.

5. Conclusions

In this paper, a proposed model for influenza virus with both resistance and non - resistance to Oseltamivir is introduced. The Basic Reproduction Ratios R_0^1 and R_0^2 that determines the propagation dynamics of the disease is determined. When $R_0^1 \le 1$ and $R_0^2 \le 1$ the system has only a disease free equilibrium E_0 which is globally asymptotically stable. When $R_0^1 > 1$ and $R_0^2 > 1$ then the system has endemic equilibria E_1 and E_2 which are globally asymptotically stable. Global stabilities were determined using Lyapunov functions.

References

1. Zambon MC. Epidemiology and pathogenesis of influenza. *Journal of Ant microb Chem* 1999; **448**: 3-9.
2. Dawood F S, Luliano A D, Reed C, Martin I M, David K S, Po-Young C, Don B, Robert B, Brooks W A, Buchy P, Feikin R F, Fowler K B, Gordon A, Hien NT, Horby P, Huang SQ, Kartz MA, Krishnan A, Lal R, Montgomery JM, Molbak K, Pebody R, Presanis AM, Razuri H, Steens A, Tinoco Y O, Wallinga J, Yu H, Vong S, Bresse J, Widdowson M. Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation. *A Modelling Study. Lancet Infect Dis* 2012; **12(9)**: 687-695.
3. Ju B, Bindumadhav M, Enlena AG, Jie JZ. Drug repurposing identifies inhibitors of Oseltemivir- resistant influenza virus. *Angew. Chem* 2016; **128**: 3499-502.
4. Bulletin of WHO. *A revision of the system of nomenclature for influenza viruses: a WHO Memorandum* 1980; **58(4):** 585-91.
5. Nguyen HK. Stability analysis of an influenza virus model with disease resistance. *J Egypt Mathl Soc* 2016; **24**: 193-199.
6. Brian JC, Bradley GW, Sally B. Modelling influenza epidemics and pandemics insights to the future of Swine flu (H1N1). *MBC Med* 2009.

7. Carr S, Ilyushina NA, Franks J, Adderson E, Caniza M, Govorkova EA, Webster RG. Oseltamivir- resistant influenza A and B viruses pre- and postantiviral therapy in children and young adults with cancer. *Ped Infect Dis J* 2011; **30(4)**: 284-8.
8. Neil MF, Susan M, Helen J, Noel R, Penelope W. A population dynamics model for evaluating the potential spread of drug- resistant influenza virus infection During Community- Based Use of Antivirals. J. Antimicrob. Chemother 2003; **51**: 977- 90.
9. Fraser C, Christl AD, Simon C, William PH, Maria DVK, Hollingworth TD, Jamie G, Rebecca FB, Helen EJ, Emiley JL, Thibaut J, Wes RH, Nicholas CG, Francois B, Azra CG, Neil MF, Andrew R, Oliver GP, Hugo LG, Celia MA, Letza BC, Ethel PZ, Dulce MEG, Francesco C, Erika G, Stephane H, Cathy R. Pandemic potential of a strain of influenza A (H1N1). *Early finding. Science* 2009; **324**: 1557- 61.
10. Coburn BJ. *Multi- species influenza models with recombination. PhD Dissertation Coral Gables*. University of Miami; 2009.
11. Krobeinikon A, Wake GC. Lyapunov functions and global stability of SIR, SIRS and SIS epidemiological models. *Appl. Math. Lett.* 2002; **15**: 955-60.
12. Krobeinikon A. Lyapunov functions and global properties for SEIR and SEIS epidemic models. *Math Med Biol* 2004; **21**: 75-83.
13. Driessche P, Watmough J. Reproduction numbers and sub- threshold endemic equilibria for compartmental models of disease transmission. *Math Biosci* 2002; **180**: 29-48.